REMARKS

Claims 1-24 are pending in the application. Claims 1-22 have been cancelled by this amendment. New claims 25-27 have been added to the application. Therefore, claims 23-27 are at issue.

New claims 25-27 are supported by original claim 21 and the specification at page 17, lines 10-12 and page 26, lines 5 and 6.

Claim 23 stands rejected under 35 U.S.C. §103 as being unpatentable over Orme et al. U.S. Patent No. 7,098,209 ('209) in view of *In re Hess* and *In re Henze*. Claim 24 stands rejected under 35 U.S.C. §103 as being unpatentable over Orme et al. U.S. Patent No. 6,878,711 ('711) in view of the '209 patent. Applicants traverse these rejections.

First, it is submitted that the '209 and '711 patents should be disqualified as prior art under 35 U.S.C. §103(c). At the time of invention, the subject matter of the present application, the '209 patent, and the '711 patent were subject to an obligation of assignment to the same person, i.e., Lilly ICOS LLC.

At the time of each invention, individuals from ICOS Corp., Bothell, WA, (ICOS) and Eli Lilly Co., Indianapolis, IN (Lilly) worked together to arrive at each claimed invention. In addition, all inventors were obligated to assign all inventions to Lilly ICOS LLC, an entity formed between ICOS and Lilly to conduct research and market products related to PDE5 inhibition.

To demonstrate that ICOS and Lilly cooperated in research endeavors related to PDE5 inhibition at the time of each invention, and that the inventors were obligated to assign the invention to the same entity, the present application, the '209 application, and the '711 patent each are assigned to Lilly ICOS LLC. In addition, *each* of the three inventions names inventors from ICOS *and* from Lilly, as noted from the addresses of the inventors.

In view of the above, it is submitted that the '209 patent and '711 patent should be disqualified as art under '35 U.S.C. §103(a), and that the rejection of claims 23 and 24 should be withdrawn.

It is further submitted that even if the '209 and '711 patents are citable against the present claims, claims 23 and 24 and new claims 25-27 would not have been obvious over these references under 35 U.S.C. §103(a).

Prior to addressing the cited art, applicants provide a summary of the invention because the Office Action includes statements indicating a misunderstanding of the invention. In particular, the present invention is directed to an improved method of synthesizing a *specific*, *known* compound as set forth in claim 23, i.e., Compound (I). The improved method significantly increases the amount of desired *cis*-isomer, and, accordingly, reduces the amount of undesired *trans*-isomer. One advantage of the invention is a more economical synthesis

> "because a step of separating the desired stereoisomer from the undesired stereoisomer is simplified or eliminated, and raw material wastes and costs are decreased because reactants are not consumed in the synthesis of undesired stereoisomers." (specification, page 2, lines 18-23).

Also see specification, page 1-3 for further advantages provided by an improved stereoselective synthesis of a compound.

The specific compound recited in claim 23 is a known compound, i.e., Example 78 of U.S. Patent No. 5,859,006 ('006). This synthesis is disclosed at pages 4-9 of the specification, i.e., Pathways (A) and (B). As stated in the specification at page 4, line 18 through page 4, line 6:

> "The first synthetic pathway (A), from D-tryptophan, has few steps, but the yield of the desired diastereomer (i.e., Compound II) is poor and requires a separation step from the trans-stereoisomer (Compound IIa). Pathway (A) also utilizes the highly corrosive trifluoroacetic acid (i.e., TFA or CF_3CO_2H). The key step in pathway A is a classic Pictet-Spengler reaction using D-tryptophan methyl ester and piperonal to yield substituted tetrahydro-β-carboline Compounds (II) and (IIa). The second pathway (B) provides a better yield of the desired Compound I, but requires numerous synthetic steps. In each synthetic pathway, the key intermediate in the synthesis of Compound (I) is Compound

> (II). Compound (I) then is synthesized from Compound (II) in two straightforward synthetic steps."

Also see specification, page 12, lines 16-28.

The present invention improves Pathway A to Compound (I) by increasing the yield of Compound (II) at the expense of Compound (IIa). As set forth in the specification at page 8, line 14 through page 9, line 8.

> "[T]he preparation of Compound (II) in pathway (A) utilizes a Pictet-Spengler cyclization between D-tryptophan methyl ester and piperonal in dichloromethane (CH_2Cl_2) with two equivalents of trifluoroacetic acid at 4° C. which provides, after five days, a mixture of two diastereoisomers, i.e., the desired cis-isomer tetrahydro-β-carboline Compound (II) ((1R, 3R)) and the undesired trans-isomer tetrahydro-β-carboline Compound (IIa) ((1S, 3R)) in a ratio of about 60/40. From this mixture, the pure cis-isomer (i.e., Compound (II)) can be obtained by fractional crystallization in a 42% yield (ee>99% (chiral HPLC))."

The present invention improves the stereochemical yield of Compound (I) by overcoming the disadvantages of the classic Pictet-Spengler reaction set forth in Example 78 of the '006 patent.

The improvement in the synthesis of Compound (I) utilizes a modified Pictet-Spengler cyclization reaction wherein the reaction is performed using a solvent in which only one of the diastereomers in soluble. In the method recited in claim 23 to synthesize Compound (I), this solvent is isopropyl alcohol, which provides the *cis*-isomer of the compound prepared in step (b) of Claim 23. The improved process also avoids the use of corrosive trifluoroacetic acid and the chlorinated solvent, CH_2Cl_2, both of which have toxicity issues.

The claimed synthesis of Compound (I) is set forth in the specification at page 15, line 1 through page 17, line 21. Note the use of isopropyl alcohol in step 2 providing the desired *cis*-Compound (II) in 93% yield. In contrast, compound (II) made by the method of the '006 patent resulted in only a 42% yield, with a 60/40 cis/trans ratio. The cis/trans ratio of

Compound (II) to Compound (IIa) using the present method is greater than 90/10. (See specification, page 17, lines 10-12 and page 21, lines 3-7).

The '209 patent is directed to making compounds similar to, but different from, the claimed Compound (I). The difference between the claimed Compound (I) and the compound illustrated at page 4 of the Office Action (i.e., Example 2 of the '209 patent) is the presence of a methyl group on each ring nitrogen, rather than a methyl group only at the 2-position of the ring system.

The examiner contends that the synthesis of Example 2 of the '209 patent is identical to the claimed method, with the only difference between the compounds being a methyl group, and therefore, because the compounds are homologous, the method of claim 23 would have been obvious. This line of reasoning is incorrect because a major difference exists between the claimed method and the disclosed synthesis of Example 2.

In particular, the Pictet-Spengler cyclization reaction of Example 2 of the '209 is run in refluxing isopropyl alcohol to provide Intermediate I. However, the yield of desired *cis*-isomer is only 16%, whereas the yield of undesired *trans*-isomer is 50%. The amount of *undesired* isomer therefore is 3.13 times greater than the amount of desired *cis* isomer. In contrast, the present method yields 93% of desired Compound (II) (specification, page 15, lines 10-15 and page 17, lines 10-12).

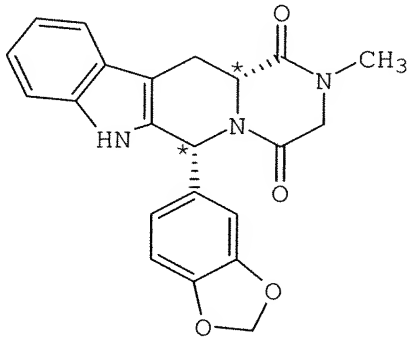
A person skilled in the art wishing to improve the yield of the desired isomer Compound (II) leading to Compound (I) would have had no incentive to utilize the method of Example 2 of the '209 patent. In fact, persons skilled in the art would avoid the method of the '209 patent because the prior method of preparing Compound (I) i.e., the '006 patent, yielded a 60/40 ratio of desired *cis* to undesired *trans* isomer (see specification, page 8, line 18 through page 9, line 8). The '209 patent, however, teaches a very poor cis/trans ratio of 24/76. Utilizing the examiner's reasoning that a person skilled in the art would expect the same results for a homologous compound, that person, after considering the poor yield and poor stereoselectivity in the preparation of Example 2 of the '209 patent, would avoid the method of the '209 patent in the preparation of Compound (I).

In contrast, even though Compound (I) may be homologous to Example 2 of the '209 patent, the present method provides a higher absolute yield of the desired Compound (II), in a much higher stereochemical selectivity. This result is totally unexpected and unpredictable from the teachings of the '209 patent.

It is submitted, therefore, that claim 23 would not have been obvious over the '209 patent, and that the rejection under 35 U.S. §103 should be withdrawn.

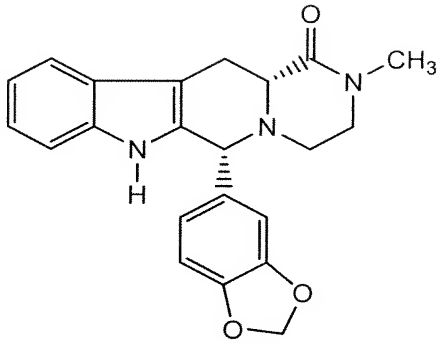
With respect to claim 24, claim 24 is a preferred embodiment of the present invention, and does not rely solely upon the features recited in claim 24 for patentability, but rather relies upon all the features of both claim 23 and 24. Therefore, it is submitted that claim 24 is patentable for the same reasons stated above with respect to claim 23, and that the rejection of claim 24 should be withdrawn.

In addition, the Office Action contains an erroneous statement. The present claims recite a "dione," i.e., has two carbonyl groups:



(Compound (I))

Contrary to the assertion in the Office Action, Example 1 of the '711 patent is *not* identical to Compound (I). Example 1 of the '711 patent is not a "dione" as it includes only *one* carbonyl group:



In summary, for all the reasons set forth above, it is submitted that claim 24 would not have been obvious over a combination of the '209 and '711 patents, and that the rejection should be withdrawn.

It is further submitted that new claims 25-27 also would not have been obvious over a combination of the '209 and '711 patents for the reasons set forth above with respect to claims 23 and 24.

All claims are in a condition and form for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

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Respectfully submitted,

By _____

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